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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/259,658	02/26/99	COLYER J	04256/79245

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EXAMINER	
PORTNER, V	
ART UNIT	**PAPER NUMBER**
1645	10

DATE MAILED: 08/17/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant
09/259,658	Coyler et al
Examiner	**Group Art Unit**
Portner	1645

X Responsive to communication(s) filed on _____

This action is **FINAL.**

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

X Claim(s) 1-18 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

Claim(s) _____ is/are allowed.

X Claim(s) 1-18 is/are rejected

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-18 are pending. Claim 19 has been canceled.

Sequence Letter

1. The instant application is now in sequence compliance.

Election/Restriction

2. Applicant's election without traverse of Group I, claims 1-18 drawn to method of analyzing a sample, classified in class 435, subclass 7.21, in Paper No. 8 is acknowledged.

Information Disclosure Statement

3. The 1449 paper listing of references on the information disclosure statement filed March 2, 2000 was matched with the instant Application but no referencesaccompanied the paper. Therefore, the references were not considered prior to first action. Applicant's Representative, Ms. Williams was notified of this fact by phone, on August 9, 2000.

Please Note: No specific functional characteristics of the polypeptides are recited in the claims other than they have the capability of associating with each other. The modification recited in claims 1-12 is being read to be the formation of a two polypeptide association complex that would have a dissociation constant. The word "modulation" is being read to include the binding of the two polypeptides to each other and that may dissociate, which is a type of modulation of the components of the complex as no specific type of modulation is recited in the claims.

Claim Rejections - 35 U.S.C. § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-4, 6,8,12-14, 16, 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1 is a method of analyzing a sample. No sample has been provided. The claim only provides two polypeptides. The polypeptides are not defined as the sample. Clarification is requested. The subsections of the claim are numbered. This is confusing because each of the claims are numbered with the same type of numbers. Removal of the numbering for the subsections of the claim could make it clearer.

b.Claims 2-4 recites the phrase "the binding partner". This phrase lacks antecedent basis in claim 1 that only defines first and second polypeptides. The first polypeptide being immobilized. Clarification is requested.

c. Claim 4 depends from claim 3 and recites the phrase "said labels". This term lacks antecedent basis in claim 3 that only recites the presence of a single label.

d.Claim 6 recites the phrase "said detectable signal", this phrase lacksantecedent basis in claims 3 and 4. Claim 6 also recites the phrase "between the labels" and depends from claim 3. This phrase lacks antecedent basis in claim 3.

e.Claim 8 recites the phrase "the hybrid species". This phrase lacks antecedent basis in claim 1 from which it depends.

f.Claim 12 recites a "wherein" clause. This does not define an active methods step. The nature and type of antibody is not defined. Which of the polypeptides or the product of the polypeptides the antibodies bind is not distinctly claimed. How the antibody interacts with the

polypeptides to produce a measurement is not clear from the use of any type of antibody that need not be specific to any of the components of the assay or sample of claim 1.

g. Claim 13 depends from claim 1 and recites the phrase "prior to step (d)". No step (d) is recited in claim 1. This phrase lacks antecedent basis in claim 1. The agent used to modify one or both of the polypeptides is not defined. The agent is being read to encompass the physical support because it is added prior to the fourth step, in which the first polypeptide is immobilized which results in a modification of the first polypeptide. What functional characteristics or types of modifications the agent has is not distinctly claimed.

h. Claim 14 defines a characteristic of the immobilized polypeptide. The immobilized polypeptide has already been modified through immobilization. What other types of modification of the first polypeptide is not distinctly claimed. The definition of a characteristic of the immobilized polypeptide does not define an additional methods step, when the type of "susceptible" modification is not distinctly claimed. All polypeptides are susceptible to modification by heat, chemicals and enzymes. What type of susceptibility is being recited is not distinctly claimed.

i. Claim 16 depends ~~form~~ from claim 1 and recites the phrase"modification of step(d)". This phrase lacks antecedent basis in claim 1. Claim 16 does not recite a proper Markush group. How the assaying is measured is not distinctly claimed.

j. Claim 18 recites two detecting steps for modulation of binding of the polypeptides. It is not clear whether the first and second detecting steps are one in the same. The second detecting

modulation appears that it should be detection in the presence of the candidate modulator. Clarification of the different types of modulation of the polypeptide binding is requested.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

5. Claims 1-8, 12-14, 16,18 are rejected under 35 U.S.C. 102(e) as being anticipated by Bronstein et al (US Pat. 5,849,495).

(Claim 1) Bronstein et al disclose a method of analyzing a sample for the presence and amount of a biopolymer in the sample, wherein the method comprises providing a polypeptide pair, specifically steptavidin and biotin (see col. 16, lines 31-57).

In one embodiment detection of biotinylated DNA is accomplished through energy transfer.

(claim 1) Biotinylated DNA was spotted on to Pall Biodyne A nylon membrane (see col 16, example 4, lines 34-35)

(claim 1 and claim 2) and subsequently contacted with a second polypeptide, streptavidin labeled with alkaline phosphatase (see col. 16, lines 31-32).

(claim 1, 5-7) Addition of a substrate for the labeled streptavidin produced a fluorescent color through energy transfer ~~form~~ from CSPD to AttoPhos(TM) (see col. 16, lines 5-6). Both blue and green fluorescent colors were produced based upon the donor and acceptor energy transfer (see col. 16, lines 5-27).

In a second embodiment, the reference discloses the use of a Hybritech Prostate Specific Antigen(PSA) kit for the determination of the presence and amount of PSA in a sample.

(Claim 1-7, 12-14, 16,18) Three polypeptides were provided. One being the PSA standard, the second being an alkaline phosphatase labeled mouse antibody and a third being an anti-PSA capture antibody immobilized on a bead.

(Claims 2-4) Both the antibody polypeptides are labeled, wherein one label is alkaline phosphatase and the other a bead.

(Claims 5-7) The association of the alkaline phosphatase labeled antibody with two different substrates resulted in the production of fluorescence and energy transfer from ~~on~~ one modified component to another.

(Claim 12-14, 16 and 18) One of the antibodies was modified with alkaline phosphatase and one was immobilized prior to each of the polypeptides being brought into proximity for association with each other. The production of a three polypeptide complex resulted in a modification of each of the members of the sample. The modification was assayed through the presence of the alkaline phosphatase label producing two fluorescent colors due to the presence of two different

substrates being added. Clearly the immobilized polypeptide was susceptible to modification through association of specific binding of PSA in the sample, as well as specific binding of the second polypeptide to the first polypeptide indirectly through the presence of PSA in the sample. Dephosphorylation of one substrate resulted in increase energy transfer and increased signal production (col. 16, lines 12-14).

(Claim 1,2,3,8,14,16) A third embodiment is disclosed, wherein a first polypeptide is immobilized in either nitrocellulose or PVDF (see Example 1, col. 14, lines 18-67 and top of col. 15).

The first polypeptide once immobilized through electrophoresis(allowing the measurement of the molecular mass of the components, claim 8 limitations) and electrotransfer was contacted with a second polypeptide that was labeled with alkaline phosphatase. Upon association with a substrate for alkaline phosphatase, the presence of binding between the two polypetides was measured through the association of the two polypeptides and the enzyme substrate. The association resulted in the production of a fluorescent signal that was measured using a CCD image camera interface and an Apple Macintosh Iici computer (see col. 14, lines 47-53).

The reference anticipates the now claimed invention.

6. Claims 1-7,14-16,18 are rejected under 35 U.S.C. 102(b) as being anticipated by Tsien et al (5,439,797) .

Tsien et al disclose and claim a method of determining the concentration of an analyte in a sample. The method is carried out by utilizing first and second polypeptides that will associate (col. 5, lines 15-16 and col. 6, lines 27-49) with each other depending upon the

presence, absence or amount of analyte present in the sample. Both the first and second polypeptides are fluorescently labeled and the modification of the association of the first and second polypeptides is accomplished through fluorescence energy transfer (see claims 15, 19 and 20). The presence of a physical support is claimed in the method of analyzing a sample, wherein the physical support is a bead (see claims 19 and 32; col. 6, line 64). The bead is used in the methods step of contacting the first and second polypeptides with the sample. The bead defines a solid phase to which the first polypeptide would be associated. This association is a type of immobilization which results in the introduction of the first and second polypeptides into cells. As no specific type of immobilization is recited in the claims, the association defines the immobilization may be non-covalent association/immobilization. Measurement of the association of the first and second polypeptides is done with real time readings within the cell (see claim 18, and col.6, line 53). The reference inherently anticipates the now claimed invention.

7. Claims 1-7, 13-16 are rejected under 35 U.S.C. 102(e) as being anticipated by Tsien et al (US Pat.5,981,200).

Tsien et al disclose tandem fluorescent protein constructs (col. 11, lines 28-46, col. 16, lines 20-58) for use in enzymatic assays conducted in 96 well microtitre plates (see col. 24, lines 63-67 to col. 25, lines 1-4 and Figure 9). The reagents would associate with the surfaces of the 96 well plate and therefore would be immobilized on the solid phase (col. 20, lines 47-54). As no specific type of immobilization of the first polypeptide is claimed, the disclosure of Tsien et al inherently teaches the use of a physical support on which the assay reagents can be immobilized.

Two different fluorescent labels are used in the assay method and are used in evaluating protease activity present in a sample (see col. 7, lines 26-27, col. 7, lines 35-37, col. 8, lines 1-20; col. 19, lines 1-46 and Section III, starting at col. 19 through col. 22). The reference teaches methods of assaying modulation of a functional property of an enzyme polypeptide or polypeptide receptor (col.22, lines 16-31 and col. 5, lines 50-67). Real time assay measurements are taught, through imaging dynamic non-covalent protein-protein associations in situ (col. 25, lines 5-17 and col. 26, lines 1-2).

8. Claims 1-7,14 are rejected under 35 U.S.C. 102(b) as being anticipated by Lakowicz et al (US Pat. 5,631,169).

Lakowicz et al disclose the use of polymeric supports for one reactant bound thereto and a second reactant that is supplied to the support in solution or suspension (col. 2, lines 49-51). The reference teaches the evaluation of blood, urine and secretions, as well as whole blood and living tissues samples (col. 3, lines 47-48) using both in vivo and in vitro methods of analyzing a sample. The samples are analyzed using first and second polypeptides, specifically first and second antibodies, one of which would be immobilized on a solid phase (claims 21 and 22). Each of the polypeptides are labeled with different fluorescent labels that provide for assaying the modification of the polypeptides through the determination of the presence or absence of an antigen in the sample. Through binding of the antibody polypeptides to the antigen, modification of fluorescence is accomplished through energy transfer (see col. 1, lines 50-59). Inherently the reference anticipates the now claimed invention.

9. Claims 1-6,10-14, 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Gallatin et al (US Pat 5,989,843 or. 5,837,822).

Gallatin et al disclose methods of analyzing samples utilizing a first polypeptide (shICAM-R) immobilized on a solid phase ('843 and '822:col. 25, to col. 26,) that interacts with a detectably labeled nonimmobilized binding partner. A agent test compound is added to the assay, wherein the presence or absence of label bound is correlated with the ability of the agent to inhibit ICAM-R binding('843col. 25, lines 60-67).

The use of fluorescent polystyrene beads is disclosed for the immobilization of a first polypeptide ('843, see col. 26, line 6) and the second polypeptide is labeled with a radio active label that is use in a scintillation proximity assay for the identification of modulators of the first polypeptide's association with the second polypeptide. The specific agent disclosed was an anti-CD18 antibody and the ability of the agent to block leukointegrin binding was analyzed. Modulators of ICAM-R binding are taught to be identifiable using the methods disclosed. The reference inherently anticipates the now claimed invention.

10. Claims 1 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Sehr (US Pat. 5,341,215).

The reference claims an apparatus to which biomolecules are attached for conducting surface plasmon waves (see claim 19 and col. 7, lines 41-46; col. 6, lines 44-49), as well as a method of analyzing a sample for the presence of biomolecules. The method comprises the use of a solid phase coated with capture molecules complementary to the biomolecules (see

claims 1-13). The types of biomolecules disclosed are those known to be detectable by immunoassay (see col. 1, line 35), specifically antigen and antibody reactions (see col. 2, line 9) and DNA. The mode of detecting the interaction of an antibody (a first polypeptide) and the corresponding antigen (proteins are known antigens, a second polypeptide) is based upon surface plasmon resonance (col. 2, lines 11-12). Immobilization of the antibody to the physical support would be carried out when the sample is being analyzed for antigen and in the case where the sample is being analyzed for antibody the antigen would be immobilized on the immunosenor.

Their exemplified embodiment utilizes labeled DNA that competes with the components in the sample being analyzed for binding to an immobilized biomoleulce on the solid phase, but the method disclosed other kinds of biomolecules as well (col. 9, lines 17-21). A labeling process for the DNA comprised the use of complimentary polypeptides: biotin that is incorporated into the DNA that is subsequently reacted with labeled avidin (col. 7, lines 41-46) The immobilization and contacting steps are simultaneously carried out through a competition between the complementary biomolecules in solution, one of which is labeled through the use of biotin and avidin, the other being the biomolecule to be detected. Through binding of the labeled biomolecule to the complementary biomolecule immobilized, immobilization of the first and second polypetides is accomplished. Assaying modulation of the interaction of the first and second reactants, one of which is labeled, is accomplished through measuring the variation of reflectivity or resonance shift (see col. 2, lines 35-50) on the surface plasmon resonance sensor. The disclosure inherently anticipates the now claimed method.

11. Claim 17 is rejected under 35 U.S.C. 102(b) as being anticipated by Decher et al (US Pat. 5,208,111).

Decher et al disclose a polypeptide pair immobilized to a support, wherein the second polypeptide is bound to the first polypeptide(see figures 10-11; Figures 3-12, col. 3, lines 58-68 and col. 4, lines 1-15). The two polypeptides disclosed are poly-Lysine and the second is biotin. The immobilized first polypeptide bound by the second polypeptide is modulated when they come into contact with heat and solvents (col. 2, lines 47-55) and show greater mechanical and thermal stability than other types of supports to which polypeptides have been immobilized, as well as through binding of streptavidn that is fluorescently labeled (see example 17, col. 20).

12. Claim 17 is rejected under 35 U.S.C. 102(e) as being anticipated by Mills (US Pat. 5,773,592).

Mills disclose a polypeptide pair immobilized to a support, wherein the second polypeptide is bound to the first polypeptide (see claims 24-26) The two polypeptides disclosed are an enzyme immobilized (claim 24) covalently bound to either insulin(claim 25) or tissue plasminogen activator(claim 26). Modulation of a chemiluminescent through energy transfer and photochromic excitation (see claim 1) is in association with the first and second polypeptides. The reference inherently anticipates the now claimed invention.

Conclusion

13. This a non-final action. No claims are allowed.

14. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

15. Gallatin et al (US Pat. 5,880,268) is cited to show modulators of ICAM-R.

16. Aversa et al (US Pat.5,977,303) is cited to show SLAM protein.

17. DE 43 19 037 is cite to show a support upon which is immobilized a first polypeptide to which a second polypeptide is bound, wherein the first and second polypeptides are associated with first and second fluorescent labels for use in determining fluorescence ratios of Foster energy transfer in an assay of determining an analyte. Modulation of fluorescence is effected through analyte binding (see page 14, claim 10), and teaches the use of energy transfer through first and second fluorescent labels taught by Hugl et al (US Pat. 5,194,393)).

18. Davis et al (US Pat. 5,484,735) is cited to show an immunoassay for a glycoslyated protein using immobilized whole cell antigen on a solid phase.

19. Vierstra et al (US Pat. 5,851,791) is cited to show the use of first and second polypeptides in a process of using an ubiquitin-conjugating enzyme.

20. Ibanez et al (US Pat. 5,891,638, 5,976,815) are cited to show serine threonine receptor ALK-7.

21. Delvecchio (US Pat. 6,010,848) is cited to show methods of screening for agonists and antagonists for an ATPase protein from Hepatitus C virus.

22. Vlassara et al (US Pat. 5,316,754) is cited to show the use of immobilized reagents to detect the presence of advance glycosylated end products.

23. Beach et al (US Pat. 6,001,619) is cited to show ubiquitin ligases and their use.

24. Beach et al (US Pat. 6,037,136) is cited to show a method of screening for inhibitors for phosphatases.

25. Sato et al (US Pat. 4,478, 934) is cited to show an immunoassay for the determination of adenosine through the acylation of adenosine.

26. Lee (US Pat. 5,795,729) is cited to show an energy transfer fluorescent probe for detecting a reagent in a sample.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp
August 8, 2000

L. F. Smith

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